PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 17685PCTAP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/007015	International filing date *(day/month/year)* 03 March 2005 (03.03.2005)	Priority date *(day/month/year)* 11 March 2004 (11.03.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALLERGAN, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 September 2006 (13.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Athina Nickitas-Etienne e-mail: pt04@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/007015	03.03.2005	11.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/4439, A61K38/06, A61P1/04, A61K31/4704

Applicant
ALLERGAN, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion.
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

Loher, F

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007015

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007015

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15 (IA)

because:

☒ the said international application, or the said claims Nos. 1-15 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15,18,19,22,24
	No:	Claims	16,17,20,21,23
Inventive step (IS)	Yes:	Claims	8,12,14,21,23
	No:	Claims	1-7,9-11,13,15-20,22,24
Industrial applicability (IA)	Yes:	Claims	16-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DIETRICH C G ET AL: "ABC of oral bioavailability: Transporters as gatekeepers in the gut." GUT, vol. 52, no. 12, December 2003 (2003-12), pages 1788-1795, XP009051184 ISSN: 0017-5749

D2: PAULI-MAGNUS CHRISTIANE ET AL: "Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 364, no. 6, December 2001 (2001-12), pages 551-557, XP002337738 ISSN: 0028-1298

D3: IM W B ET AL: "REVERSAL OF ANTISECRETORY ACTIVITY OF OMEPRAZOLE BY SULFHYDRYL COMPOUNDS IN ISOLATED RABBIT GASTRIC GLANDS" BIOCHIMICA ET BIOPHYSICA ACTA, vol. 845, no. 1, 1985, pages 54-59, XP002337739 ISSN: 0006-3002

D4: MORIYAMA YOSHINORI ET AL: "Evidence for a common binding site for omeprazole and N-ethylmaleimide in subunit A of chromaffin granule vacuolar-type H+-ATPase" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 196, no. 2, 1993, pages 699-706, XP002337740 ISSN: 0006-291X

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 16 and 17 is not new.

D2 discloses a combination comprising omeprazole and the MDR-1 inhibitor PSC833. Therefore, the subject-matter of claim 16 is not new in the light of D2.

D3 discloses a combination comprising omeprazole and glutathione. Therefore, the subject-matter of claims 16 and 17 is not new in the light of D3.

D4 discloses a combination comprising omeprazole and glutathione. Therefore, the subject-matter of claims 16 and 17 is not new in the light of D4.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1, 3, 4, 5, 7, 9-11, 13, 15-20, 22 and 24 does not seem to involve an inventive step.
D1 discloses the use of MK571 as inhibitor of MRP2. D2 discloses a combination comprising omeprazole and the MDR-1 inhibitor PSC833.
The problem to be solved by the present invention may therefore be regarded as how to provide an improved medicament for the treatment of gastric acid related diseases.
The present application suggests to solve the problem posed by providing a combination comprising a proton pump inhibitor (PPI) or prodrug thereof and a compound which modulates the activity of an efflux transporter protein of the gastrointestinal epithelium.
D3 and D4 teach that glutathion antagonizes omeprazole efficacy by reactivating omeprazole-inhibited proton pumps.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 16 and 17 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 1, 3, 4, 5, 7, 9-11, 13, 15, 18-20, 22 and 24 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel over the prior art contribute to the solution of the posed problem. To use prodrugs of a compound is considered to be a routine option in the field of pharmacology. There is no particular surprising effect resulting from that choice.
With respect to the use of a efflux transporter stimulating compound in particular glutathione, it is at present not clear wherein a desirable effect may rely. The present application demonstrates that inhibiting MRP2 is useful with respect to administration of PPIs. Why should be a compound that exerts the opposite effect be useful? In addition, it is clear from the teaching of D3 and D4 that in fact glutathion antagonizes the efficacy of omeprazole.

It is therefore noted, that the solution proposed in claims 1, 3, 4, 5, 7, 9-11, 13, 15-20, 22 and 24 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 16-24 is considered to be industrially applicable in the sense of Art 33(4) PCT.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/007015	International filing date *(day/month/year)* 03.03.2005
Priority date *(day/month/year)* 11.03.2004	
International Patent Classification (IPC) or both national classification and IPC A61K31/4439, A61K38/06, A61P1/04, A61K31/4704	
Applicant ALLERGAN, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
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If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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For further options, see Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007015

Box No. I Basis of the opinion

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2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

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3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007015

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15 (IA)

because:

☒ the said international application, or the said claims Nos. 1-15 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/007015

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15,18,19,22,24
	No:	Claims	16,17,20,21,23
Inventive step (IS)	Yes:	Claims	8,12,14,21,23
	No:	Claims	1-7,9-11,13,15-20,22,24
Industrial applicability (IA)	Yes:	Claims	16-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

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D1: DIETRICH C G ET AL: "ABC of oral bioavailability: Transporters as gatekeepers in the gut." GUT, vol. 52, no. 12, December 2003 (2003-12), pages 1788-1795, XP009051184 ISSN: 0017-5749

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D4 discloses a combination comprising omeprazole and glutathione. Therefore, the subject-matter of claims 16 and 17 is not new in the light of D4.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1, 3, 4, 5, 7, 9-11, 13, 15-20, 22 and 24 does not seem to involve an inventive step.
D1 discloses the use of MK571 as inhibitor of MRP2. D2 discloses a combination comprising omeprazole and the MDR-1 inhibitor PSC833.
The problem to be solved by the present invention may therefore be regarded as how to provide an improved medicament for the treatment of gastric acid related diseases.
The present application suggests to solve the problem posed by providing a combination comprising a proton pump inhibitor (PPI) or prodrug thereof and a compound which modulates the activity of an efflux transporter protein of the gastrointestinal epithelium.
D3 and D4 teach that glutathion antagonizes omeprazole efficacy by reactivating omeprazole-inhibited proton pumps.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 16 and 17 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 1, 3, 4, 5, 7, 9-11, 13, 15, 18-20, 22 and 24 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel over the prior art contribute to the solution of the posed problem. To use prodrugs of a compound is considered to be a routine option in the field of pharmacology. There is no particular surprising effect resulting from that choice.
With respect to the use of a efflux transporter stimulating compound in particular glutathione, it is at present not clear wherein a desirable effect may rely. The present application demonstrates that inhibiting MRP2 is useful with respect to administration of PPIs. Why should be a compound that exerts the opposite effect be useful? In addition, it is clear from the teaching of D3 and D4 that in fact glutathion antagonizes the efficacy of omeprazole.

It is therefore noted, that the solution proposed in claims 1, 3, 4, 5, 7, 9-11, 13, 15-20, 22 and 24 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 16-24 is considered to be industrially applicable in the sense of Art 33(4) PCT.